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09/765,301	01/22/2001	Michal Eisenbach-Schwartz	EISENBACH-SCHWARTZ=18	8567

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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/765,301	Applicant(s) EISENBACH-SCHWARTZ ET AL.	
	Examiner Bridget E. Bunner	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *2-6,9,15-19,21,23,26-29,32,38-42 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,8,10-14,20,22,24,25,30,31,33-37,43,44 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-46* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 23 January 2003 (Paper No. 12) has been entered in full. Claims 1, 3, 7-20, 26, 30-43, and 45-46 are amended.

This application contains claims 2-6, 9, 15-19, 21, 23, 26-29, 32, 38-42, and 45 drawn to an invention nonelected without traverse in Paper No. 9 (13 May 2002). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

As indicated in the previous Office Action (Paper No. 11, 30 July 2002), Applicant elected Group IV, claims 20-25 and 30-42 in Paper No. 9 (13 May 2002). However, since Applicant did not distinctly and specifically point out the errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The Examiner acknowledges that Applicant did state new independent claim 43 is a generic linking claim (see pg 5-6 of the Response of 13 May 2002, Paper No. 9). However, Applicant did not specifically explain why any of the four restricted groups should be rejoined to the elected Group IV, without mention of the linking claim. It is not clear to the Examiner how Applicant's discussion of the linking claim translates into a traversal of the four separate groups. Applicant explains that since the linking claim is generally directed to a method for inhibiting neuronal degeneration caused or exacerbated by glutamate toxicity in the CNS by causing Cop 1 activated T cells to accumulate

at the site of degeneration, the methods of all of the claims should be examined. However, Applicant did not specifically explain to the Examiner why, for example, Group I should be rejoined to Group IV. Secondly, claim 43 is only being examined to extent that it reads on the elected invention and species. If claim 43 is eventually found to be allowable, consideration of rejoining the other groups will be given.

It is noted to Applicant that in the previous Office Action (Paper No. 11, 30 July 2002), the Examiner erroneously stated which groups were rejoined from the restriction requirement. The Examiner stated that Groups I and IV were rejoined. The Examiner actually rejoined Groups II and IV as evidenced by the claims examined and the rejections that were made of record. Groups II and IV were rejoined because both groups contain claims that recite the administration of Cop 1 or a Cop 1 related polypeptide to an individual.

Furthermore, if the election of Group IV had been treated with traverse, the traversal most likely would have been found persuasive *in part* by the Examiner. Specifically, Groups I and III would have been rejoined because both groups contain claims that recite the administration of T cells activated by Cop 1 or a Cop 1-related peptide to an individual. However, Groups I/III and Groups II/IV would not have been rejoined together. Groups I/III require search and consideration of efficacy of therapy of administration of Cop 1 activated T cells while Groups II/IV require search and consideration of efficacy of therapy of administration of Cop 1 protein. Searching the inventions of Groups I/III and II/IV together provide an undue search burden on the examiner because of the non-coextensive nature of these searches.

The Examiner also concedes that claim 7 was erroneously withdrawn from examination. Therefore, claim 7 has been rejoined with the previously examined claims. It is also noted that

claims 11-14 and 34-37 have been rejoined to the examined claims due to Applicant's claim amendments.

Since the restriction requirement was made final in the previous Office Action (Paper No. 11, 30 July 2002), if Applicant wishes to pursue the matter further, a petition should be filed in accordance with 37 CFR 1.144.

Claims 1, 7-8, 10-14, 20, 22, 24-25, 30-31, 33-37, 43-44, and 46 are under consideration in the instant application as they read upon the elected species of Cop 1, disease, and glaucoma.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 3 of the previous Office Action (Paper No. 11, 30 July 2002) are *withdrawn in part* in view of the amended specification (Paper No. 12, 23 January 2003). Please see section on Specification, below.

2. The rejections of claims under 35 U.S.C. § 112, second paragraph as set forth at pg 6-7 of the previous Office Action (Paper No. 11, 30 July 2002) are *withdrawn in part* in view of the amended claims (Paper No. 12, 23 January 2003). Please see section on 35 U.S.C. § 112, second paragraph, below.

3. The rejection of claim 1 under 35 U.S.C. § 102(b) as set forth at pg 7 of the previous Office Action (Paper No. 11, 30 July 2002) is *withdrawn* in view of the amended claim (Paper No. 12, 23 January 2003).

4. The rejection of claims 20, 30-31, and 33 under 35 U.S.C. § 103(a) as set forth at pg 8-9 of the previous Office Action (Paper No. 11, 30 July 2002) is *withdrawn* in view of the amended claims (Paper No. 12, 23 January 2003).

Specification

5. The objection to the disclosure regarding a suggested title change is maintained and held in abeyance until all other issues are resolved.

Claim Objections

6. The objection to claims 1, 8, 10, 20, 22, 30-31, 33, 43-44, and 46 for reciting non-elected species and groups maintained and held in abeyance until the elected species are found allowable.

Claim Rejections - 35 USC § 112

7. Claims 1, 7-8, 10-14, 20, 22, 24-25, 30-31, 33-37, 43-44, and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting secondary neuronal degeneration of ganglion cells caused or exacerbated by glutamate toxicity in the central nervous system (CNS) comprising administering to an individual with glaucoma an effective amount of Copolymer 1 (Cop 1) to inhibit secondary neuronal degeneration, does not reasonably provide enablement for a method for protecting CNS cells from glutamate toxicity or for treating any disease caused by glutamate toxicity by administering Cop 1. The specification also does not provide enablement for a method of inhibiting neuronal degeneration caused or exacerbated by glutamate toxicity in the CNS of an individual in need thereof, comprising causing activated T cells, which have been activated by Cop 1, to accumulate at the site of neuronal degeneration in the individual in need. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or the invention commensurate in scope with these claims.

Claims 1, 7-8, 10-14, 20, 22, 24-25, 30-31, 33-37, 43-44, and 46 recite a method for protecting CNS cells from glutamate toxicity, which comprises administering to an individual in need thereof an effective amount of Cop 1, thereby protecting CNS from glutamate toxicity, with the proviso that the individual in need is other than one who has multiple sclerosis. The claims recite a method for treating disease caused or exacerbated by glutamate toxicity, which comprises administering to an individual having a disease an effective amount of Cop 1 with the proviso that the individual having a disease caused by glutamate toxicity is other than one who has multiple sclerosis. The claims are directed to a method for inhibiting neuronal degeneration caused or exacerbated by glutamate toxicity in the CNS of an individual in need thereof, comprising causing activated T cells, which have been activated by Cop 1, to accumulate at the site of neuronal degeneration in the individual, thereby inhibiting neuronal degeneration at the site, with the proviso that the individual in need is other than one who has multiple sclerosis. The claims also recite that Cop 1 is administered in a manner which promotes active immunization of the individual so as to build up a critical T cell response.

Applicant's arguments (Paper No. 12, 23 January 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that with respect to which cell types are inhibited from neuronal degeneration, the cell type is neurons. Applicant states that the present claims are clear in this regard.

Applicant's arguments have been fully considered but are not found to be persuasive. Although the cell types recited in the instant claims are CNS cells and neurons, there are a variety of neurons/CNS cells encompassed by the claimed methods, such as motor neurons,

sensory neurons, glial cells, dopaminergic neurons, serotonergic neurons, oligodendrocytes, Schwann cells, and astrocytes. As discussed in the previous Office Action, the specification only teaches that the number of surviving retinal ganglion cells in the Cop 1-immunized rats is significantly higher than in the PBS injected controls (pg 83, lines 1-4; Figure 11A-C). A large quantity of experimentation would be required by the skilled artisan to inhibit neuronal degeneration of all possible CNS cells or neurons wherein the degeneration is caused or exacerbated by glutamate toxicity. Undue experimentation would also be required of those of skill in the art to protect all CNS cells or neurons from glutamate toxicity. The method of administering Cop 1 in the specification is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

(ii) Applicant argues that if secondary neuronal degeneration is inhibited and there is an ongoing insult to the neurons, i.e., on-going primary degeneration, it would be expected that the primary degeneration would be inhibited in the same way that the secondary degeneration is inhibited. Applicant contends that the examiner has not set forth any reason why one of skill in the art would not expect that the presently-claimed treatment would also inhibit primary neuronal degeneration.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the specification does not teach any methods or working examples that indicate an inhibition of "primary" neuronal degeneration caused or exacerbated by glutamate toxicity in CNS by administration of Cop 1 to an individual. The specification teaches that "a catastrophic consequence of central nervous system injury is that the primary damage is often compounded

by the gradual secondary loss of adjacent neurons that apparently were undamaged, or only marginally damaged by the initial injury"(pg 3, last ¶). The specification also discloses that "neurons in the central nervous system do not undergo spontaneous regeneration following an injury" (pg 5, ¶ 2). As echoed by Jackowski, it is well known in this unpredictable art that regeneration does not occur in the CNS either because processes fail to grow the necessary distance, they are in competition with other nearby neuronal processes not derived from the affected nerve, astrocytic scarring blocks axonal elongation, or because of misdirected axonal growth (e.g., see Jackowski, Brit J Neurosurgery 9: 303-317, 1995; specifically pgs. 309-310 and pg. 305, last ¶). Accordingly, because of the lack of guidance provided by the specification as to how one can rescue dead or dying cells instantaneously affected, for example, by a head injury or neurodegenerative disease, there is no nexus that merely administering Cop 1 to an individual in need thereof can reasonably be extrapolated to successfully treat any human subject experiencing *"primary"* neuronal degeneration, as claimed, without undue experimentation to determine such. The examples in the specification of the instant application only indicate that administration of Cop 1 reduces *secondary* neuronal degeneration of ganglion cells caused or exacerbated by glutamate toxicity (see pg 83).

Furthermore, if secondary neuronal degeneration is inhibited and there is an ongoing insult to the neurons, one skilled in the art would not be able to predict that the primary degeneration would be inhibited in the same way that the secondary degeneration is. Relevant literature teaches that damage to the CNS is severe and irreversible, in part because of the failure of central neurons to regenerate axons (Kandel et al., Principles of Neural Science. 1991. Connecticut: Appleton and Lange; pg 264-265). Schwab et al. also indicate that "tissue damage

and functional losses after spinal cord lesion result from the initial injury, which is immediate and irreversible, and from the reactive cascade of subsequent secondary molecular and cellular processes" (Physiol Rev 76(2): 319-370, 1996; see pg 327, col 2). Schwab et al. also teach that the cascade of secondary processes is reflected in the sequence of pathological changes that take place at the lesion site within days to weeks and that are fairly independent of the nature of the primary injury (see pg 327, col 2). Therefore, one skilled in the art would not expect an inhibition of secondary degeneration to also treat primary degeneration because the art indicates the primary "insult" or degeneration is irreversible and the processes involved in secondary degeneration are separate from those of the primary injury.

(iii) Additionally, the specification does not disclose *protecting* CNS cells from glutamate toxicity by administration of Cop 1. The specification teaches that the term "neuroprotection" refers to the prevention or inhibition of degenerative effects of injury or disease in the nervous system, including protection from the secondary neurodegenerative effects which persist even when the primary risk factor is removed or attenuated. Therefore, the term "protect" as recited in the claimed methods, is interpreted as meaning that an activity will not occur, i.e. CNS cells will not die from glutamate toxicity. However, the methods in the specification only indicate a *reduction* of secondary degeneration of retinal ganglion cells subject to glutamate insult (pg 71-72, 81-83; Figures 8A-8C; 11A-11C). Undue experimentation would be required of the skilled artisan to determine the quantity of Cop 1 administered, the best route of administration, the duration of treatment, and any possible side-effects to completely protect CNS cells from glutamate toxicity.

Furthermore, the specification teaches that since Cop 1 immunization has been found useful in protecting against glutamate toxicity, it is expected that Cop 1 treatment in accordance with the present invention will be effective in the treatment of conditions, such as epilepsy, amnesia, anxiety, seizures, oxidative stress, etc (pg 45, lines 12-28). The specification also discloses that the present invention is useful for any indication, i.e., chronic or acute neurodegeneration, which is caused or exacerbated by an elevation in glutamate levels, including the early stages of ischemic stroke, Alzheimer's disease, etc. (pg 46, lines 1-8). However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. As discussed above, the specification only teaches that rats vaccinated with Cop 1 emulsified in CFA show evidence of protection of retinal ganglion cells from secondary degeneration compared to that in control rats injected with PBS (pg 83; Figure 11A-C). Therefore, undue experimentation would be required of the skilled artisan to determine the optimal dosage, duration, and route of administration of Cop 1 to reduce the neuronal degeneration caused by all possible diseases that involve glutamate toxicity, other than glaucoma. The scope of the claim 20 also encompasses a method of treating disease caused or exacerbated by glutamate toxicity, wherein the individual having the disease caused by disease is other than one who has multiple sclerosis or an autoimmune disease. The scope encompasses diseases not expected to be commensurate with the elected species of glaucoma, such as Alzheimer's disease, Huntington's disease, prion diseases, etc. (pg 44, ¶ 2). The effects encompassed by these diseases are broad and may include for example, memory loss, cognitive deficits, behavioral changes, and dementia, which effects are not commensurate with glaucoma. The etiology and pathology of glaucoma is largely dissimilar from other diseases (particularly of

the CNS) and the skilled artisan would not be able to predict that administration of Cop 1 would be beneficial for all possible diseases.

It is also noted that a broad, reasonable interpretation of the claims encompasses such diseases as Alzheimer's disease, Parkinson's disease, and Huntington's disease, among others, which have proven to be recalcitrant to treatment in the art (see for example, Halliday et al., Clin Exp Pharmacol Physiol 27: 1-8, 2000; Steece-Collier et al., Proc Natl Acad Sci USA 99(22): 13972-13974, 2002; Feigin et al. Curr Opin Neurol 15: 483-489, 2002). Therefore, undue experimentation would be required of the skilled artisan to inhibit neuronal degeneration, to treat disease or protect CNS cells in individuals by administration of Cop 1.

Proper analysis of the Wands factors was performed in the previous Office Action. Due to the large quantity of experimentation necessary to determine which cells types are inhibited from neuronal degeneration or protected from glutamate toxicity, to inhibit primary neural degeneration of any cell, and to treat all possible diseases caused or exacerbated by glutamate toxicity with Cop-1, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, unpredictability of the effects of treating diseases caused or exacerbated by glutamate toxicity with Cop 1, and the breadth of the claims which fail to recite limitations as to the type of neural degeneration caused by glutamate toxicity, the cells affected, and the disease to be treated, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, second paragraph

8. Claims 22, 24-25, and 43-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 20, 30-31, and 33-37 are indefinite because the claims do not have a step that clearly relates back to the preamble. For example, there is no step indicating that administration of Cop-1 treats disease caused or exacerbated by glutamate toxicity.

10. The term "protecting" in claims 1 and 7-8 is a relative term which renders the claims indefinite. The term "protecting" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Although the specification defines the term "neuroprotection" at pg 13, it is not clear what the term "protection" encompasses. For example, are CNS cells prevented from dying as a result of glutamate toxicity? Are CNS inhibited from dying as a result of glutamate toxicity? What effects of glutamate toxicity are the CNS cells "protected" from?

11. Claims 22, 24-25, and 43-44 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: The administration of a compound, peptide, T cells, etc. to an individual to cause activated T cells to accumulate at the site of neuronal degeneration. The basis for this rejection is set forth for claims 22, 24-25, and 43-44 at pg 7 of the previous Office Action (Paper No. 11, 30 July 2002).

Applicant's arguments (Paper No. 12, 23 January 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant states that claim 43 recites the step of "causing activated T cells...to accumulate at the site of neuronal degeneration" and that this is a positive step which includes everything that is essential. Applicant contends that the examiner's suggestion of specifying the administration of a compound, peptide or T cells relates only to mere examples of how this causing step takes place. Applicant asserts that the invention will work regardless of the means for getting the activated T cells to the site of injury.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, with respect to the elected invention, claim 43 is missing the positive step of administering Cop 1 to an individual. Since the claim does not set forth any steps involved in the method, it is unclear what method Applicant is intending to encompass. It is inappropriate to read limitations in the specification into the claims. The claims must independently define the invention for which patent protection is sought. Furthermore, the phrase "causing activated T cells" is not clear. For example, how are T cells activated against Cop 1? Does the activation "cause" the T cells to accumulate at the site neuronal degeneration?

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

BEB
Art Unit 1647
April 17, 2003

GARY KUNZ
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